

REMARKS

Claims 13 and 14 are pending in this application. By this Amendment, claims 2–12 are canceled, and claims 13 and 14 are added. Support for the amendments to the claims may be found, for example, in the claims and specification as originally filed. No new matter is added.

In view of the foregoing amendments and following remarks, reconsideration and allowance are respectfully requested.

I. Personal Interview

The courtesies extended to Applicants' representative by Examiner Pohnert at the interview held September 2 are appreciated. The reasons presented at the interview as warranting favorable action are incorporated into the remarks below, which constitute Applicants' record of the interview.

II. Objection to the Specification

The Office Action objects to the specification because it contains an embedded hyperlink and/or other form of browser-executable form, and requires that the material objected to is deleted from the specification. As indicated above, the specification is amended as required. Accordingly, reconsideration and withdrawal of the objection are respectfully requested.

III. Enablement Rejection under 35 U.S.C. §112, First Paragraph

The Office Action rejects claims 3–6 and 8–11 under the enablement requirement of 35 U.S.C. §112, first paragraph. By this Amendment, claims 3–6 and 8–11 are canceled, rendering their rejection moot. To the extent that the substance of the rejection is believed to apply to new claims 13 and 14, Applicants respectfully traverse the rejection.

A. "Any" cancer

New claim 13 is directed to, "A method for the prognosis of a human patient diagnosed with having neuroblastoma" and new claim 14 is directed to "A method for the prognosis of a human patient diagnosed with having breast cancer."

The Office Action asserts on page 10 that Maestro "contradicts the instant specification as he teaches that twist is not detectable in breast cancer." However, on page 6, the Office Action asserts that Yang teaches that twist gene expression is unregulated in breast cancer, which infers that expression of twist is found in breast cancer. In fact, Yang discloses that twist expression was detectable in human breast tumors. *See* Yang, page 935. Each of the Fackler, Stasinopoulos, and Sukamar references cited to in the Office Action discuss twist expression in breast cancer. Thus, in view of the data presented in the Applicants' specification and the disclosures of Yang, Fackler, Stasinopoulos, and Sukamar, it is respectfully submitted that Maestro's inability to find the expression of twist in breast cancer is not conclusive and does not reasonably support a lack of enablement rejection of claim 14.

B. "Any" subject

New claims 13 and 14 are directed to the "prognosis of a human patient." Thus, the Office Action's arguments found on page 11 regarding the teachings of Brenner that "a gene in two species often have different physiological response as a species have evolved in different environments" appear to be moot.

C. "Any" sample

Claim 13 recites, "obtaining a neuroblastoma sample from the patient." Support for "neuroblastoma sample" may be found in the specification, for example, at page 12, lines 20-22. Claim 14 recites, "obtaining a breast cancer sample from the patient." Support for "breast cancer sample" may be found in the specification, for example, at page 15,

lines 2–4. Because claims 13 and 14 recite specific types of samples, the arguments with respect to "any" sample present in the Office Action are moot.

D. "Any" twist gene

New claims 13 and 14 both recite "contacting the biological material with at least one reagent specific for a human twist gene." Thus, the Office Action's arguments that the claims encompass "any" twist gene, splice variant, or mutant of any species are moot.

E. "Any" expression

The Office Action asserts that twist over expression is not predictably associated with breast cancer, citing to Maestro, Yang, Fackler, Sukumar, and Kass. These arguments are moot as they are geared towards diagnosis of breast cancer, but do not reasonably relate to the prognosis of a patient already diagnosed with breast cancer.

Additionally, claims 13 and 14 recite, "comparing the expression level determined in (d) with the expression levels of the twist gene in...patients with good prognoses." Thus, expression levels are compared between the patient and the expression levels found in other breast cancer/neuroblastoma patients who had been previously determined to have a good prognosis. *See, e.g.*, Examples 1 and 2 at pages 12–16 of the specification.

F. 8th patient with poor prognosis

In response to the apparent discrepancy illustrated by the Office Action at page 4, lines 12-20, the specification indicates on page 13, lines 4-6, that the patients who had died during the study and the patients presenting a stage 4 neuroblastoma were described as patients with poor prognosis. Although not expressly stated, one of the five patients that had died during the follow-up period had not developed a stage 4 neuroblastoma. Thus, the 8 poor prognosis patients included the 7 patients with stage 4 neuroblastoma and the 1 other patient who did not have a stage 4 neuroblastoma but died during the study.

G. Normalization

The Office Action on page 5, lines 2–5, asserts that the specification provides no guidance on what measures were used to normalize expression data. However, the specification, on page 11, lines 12–21, provides the following (emphasis added):

In order to take into account the variability in enzymatic efficiency that can be observed in the various steps (reverse transcription, PCR, etc.), the expression of the twist gene of the various groups of patients can be standardized by simultaneously determining the expression of a “housekeeping” gene, the expression of which is similar in the various groups of patients. By relating the expression of the target gene to the expression of the housekeeping gene, any variability between the various experiments is thus corrected. Those skilled in the art may refer in particular to the following publications: Bustin SA *Journal of molecular endocrinology*, 2002, 29: 23-39 ; Giulietti A *Methods*, 2001, 25: 386-401.

Thus, the specification indicates that the housekeeping gene must be appropriately selected so that its expression is similar in the various groups of patients.

As established by the Office Action, it was known in the art at the time of invention the need to select appropriate housekeeping genes for normalization, and it was known that there is natural variation of gene expression among different individuals. Certainly, then, it was well known and conventional in the art at the time of invention to select appropriate housekeeping genes in view of natural variation of gene expression for a given experiment. It is well-established that not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

Thus, the question of enablement does not necessarily revolve around whether or not the specification discloses which housekeeping genes were used to normalize the data or could be used to normalize the data. Instead, the question is whether any experimentation needed to determine appropriate housekeeping genes to practice the claimed methods would

be undue. The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983).

The Office Action fails to assert that determination of appropriate housekeeping genes in order to normalize the data obtained from the claimed methods would be undue. Because it is conventional and commonplace in the art to determine appropriate housekeeping genes for any gene expression assay, Applicants respectfully submit that such experimentation would not be undue for one of skill in the art to practice the claimed methods.

H. Conclusion

For at least the reasons discussed above, Applicants respectfully submit that claims 13 and 14 meet the enablement requirement of 35 U.S.C. §112, first paragraph. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

IV. Written Description Rejection under 35 U.S.C. §112, First Paragraph

The Office Action rejects claims 3–6 and 8–11 under the written description requirement of 35 U.S.C. §112, first paragraph. By this Amendment, claims 3–6 and 8–11 are canceled, rendering the rejection moot as to those claims. To the extent that the substance of the rejection is believed to apply to new claims 13 and 14, Applicants respectfully traverse the rejection.

New claims 13 and 14 recite "human twist gene." Support for the recitation of "human twist gene" may be found, for example, in the specification at pages 20–22, which refer to H-twist (human twist). Additionally, Examples 1 and 2 implicitly disclose that the experiments determined the expression levels of human twist in the human patients. Moreover, the 5' and 3' twist primers disclosed on page 17 of the specification match 100% to the human twist gene. Lastly, the human twist gene is well known in the art, as is evident from its discussion in many of the references cited by the Office Action.

For at least these reasons, Applicants respectfully submit that one skilled in the art can reasonably conclude that the inventor had possession of the subject matter of claims 13 and 14 at the time of invention. *See* MPEP §2163. Reconsideration and withdrawal of the rejection are respectfully requested.

V. Rejection under 35 U.S.C. §112, Second Paragraph

The Office Action rejects claims 3–6 and 8–11 as being indefinite under 35 U.S.C. §112, second paragraph. By this Amendment, new claims 13 and 14 are drafted in light of the Examiner's comments. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

VI. Rejection Under 35 U.S.C. §102

The Office Action rejects claims 3–6 and 8–11 under 35 U.S.C. §102(b) over Martin et al., Breast Cancer Research and Treatment, 82(S1): S117–S118, December 3, 2005 ("Martin"). By this Amendment, claims 3–6 and 8–11 are canceled, rendering their rejection moot. To the extent that the substance of the rejection is believed to apply to new claims 13 and 14, Applicants respectfully traverse the rejection.

New claim 13 is directed to a method of prognosis for neuroblastoma. Martin makes no disclosure relating to neuroblastoma and, thus, cannot be said to anticipate claim 13.

New claim 14 is directed to a method of prognosis for breast cancer, and require:

- e. comparing the expression level determined in (d) with the expression levels of the twist gene in the breast cancers of patients with good prognoses; and
- f. determining a good prognosis or a poor prognosis based at least in part on the comparison made in (e).

Martin does not disclose such procedures and, thus, cannot be said to anticipate claim 14.

VII. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,



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